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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/786,988	01/23/1997	DANIEL P. LITTLE	24736-2001D	5922

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SAN DIEGO, CA 92130-2081

EXAMINER
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GAKH, YELENA G

ART UNIT	PAPER NUMBER
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1743

DATE MAILED: 06/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 08/786,988	<b>Applicant(s)</b> LITTLE ET AL.	
	<b>Examiner</b> Yelena G. Gakh, Ph.D.	<b>Art Unit</b> 1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 12 April 2004.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-6,9-34,40-51,54-61,63-72,78,82-94 and 102-107 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6,9-34,40-51,54-61,63-72,78,82-94 and 102-107 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>02/19/04</u> . | 6) <input type="checkbox"/> Other: _____  |

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### **DETAILED ACTION**

1. The amendment filed on 04/12/04 is acknowledged. Claims 1-6, 9-34, 40-51, 54-61, 63-72, 78, 82-94 and 102-107 are pending in the application.

#### ***Information Disclosure Statement***

2. The references cited by applicants in the IDS and listed on the numerous 1449's have been made of record. While the statements filed clearly do not comply with the guidelines set forth in MPEP 2004 regarding both the number of references cited and the elimination of clearly irrelevant art and marginally cumulative information, compliance with these guidelines is not mandatory. Furthermore, 37 CFR 1.97 and 1.98 do not require that the information be material, rather they allow for submission of information regardless of its pertinence to the claimed invention. Also, there is no requirement to explain the materiality of the submitted references, however, the cloaking of a clearly relevant reference by inclusion in a long list of citations may not comply with Applicant's duty of disclosure, see Penn Yan Boats, inc. V. Sea Lark boats Inc., 359 F. Supp. 948, 479 F. 2d. 1338.

The major part of a lengthy Supplemental IDS contains a list of US patents with wrong US patent numbers, irrelevant documents and publications (PCT), which are not the prior art for the instant application because of the publication dates.

#### ***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:  
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
4. Claims 43-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in

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the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The parent claim 40 recites “an array for dispensing a liquid therefrom, wherein each vesicle has an interior chamber containing a fluid containing the **material**” and “a mass spectrometer for analyzing **said material** deposited on said surface of said substrate, wherein mass spectra of the sample material obtained from each spot are reproducible within the array of spots”. Claims 43 and 44 recite that the fluid comprises a solvent and a **matrix material** with no recitation of the material to be analyzed. There is no way for anyone of ordinary skill in the art to obtain reproducible MALDI mass spectra for the spots, which contain only matrix, since the matrix material does not reach a mass spectrometer detector in the MALDI experiment.

***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. **Claims 1-4, 6, 9-10, 14-15, 25-28 and 30** are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (JMS Letters).

Zhang teaches a method and an apparatus for dispensing a target material on a multi-well sample holder (substrate) (Fig. 1, page 1769, line 6-8). The method comprises the steps of providing a packed capillary (i.e. vesicle) having an interior chamber containing a fluid, disposing the vesicle adjacent a first location on the surface of the substrate and ejecting a defined and controlled ~5 nL volume of the fluid, while evaporating the solvent forms a spot of the sample of less than 0.3 mm<sup>2</sup>. MALDI-MS analysis is performed directly from the spot. The chamber is rinsed with a washing solution (Figure 1, page 1768, right column). “The eluate was spotted onto a multi-well sample holder with a volume of about 5 nL per fraction”. It is absolutely clear from Figure 1 and its caption that the vesicle is moved from spot to spot to repeat these steps for each location (each well) of the multi-well holder, with ~ 5 nL of the

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sample fraction deposited in each spot. The accuracy of the volume is given exactly with the same precision as the one disclosed in the specification of the instant application: “into each well was dispensed 20 droplets (~ 5 nL) of 3-HPA matrix solution” (page 26, the last paragraph). No contacting of the vesicle with the substrate for disposing the liquid is indicated in the paper.

Reproducibility of the MALDI spectra obtained directly from the spots is intrinsic to the substrate having the same wells, the same volumes of the sample placed in the wells (~ 5 nL), the same conditions of preparing the sample for MALDI-MS analysis for each spot, and the reproducibility of the results of the “desalting/ concentration” procedure obtained from MALDI-MS analysis ( $r^2 = 0.9975$ ) (page 1769, right column, second paragraph). Zhang specifically indicates, “it is clear that sample preparation for MALDI analysis is a critical step in achieving high sensitivity and **reproducibility** for biological mixtures” (page 1771, left column). By the preparation of the sample he means removal of salts for highly salted analytes and *decreasing the volume of the sample*, with ~ 5 nL of the volume confirming high reproducibility of the experimental data, which comprise MALDI-MS spectra parameters.

### *Claim Rejections - 35 USC § 103*

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 (a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

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claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. **Claims 11-13, 29, 31-34, 40-42, 47, 51, 54-59, 61, 63-72, 82-85 and 87-94** are rejected under 35 U.S.C. 103 (a) as being unpatentable over Zhang in view of Nelson et al. (US 5,955,729).

Zhang does not specifically disclose a plurality of the vesicles forming an array, or pins with chambers delivering a solution (ink-jet applicators), and automation of the system.

Nelson discloses a surface plasmon resonance-mass spectrometry and an apparatus, which may comprise interaction analysis chip (IA chip). "In the case of IA sensor chips, a suitable matrix applicator is illustrated in FIG. 3. Matrix applicator (310) with guide pins (320) affixed thereto, is configured to accept the sensor chip affixed within a suitable chip holder (this aspect of the present invention is more fully discussed below in reference to FIG. 5). An appropriate MALDI matrix is applied to surfaces (330), (332), (334) and (336) of chip receptor (340), and the sensor chip holder (not shown) is positioned such that the individual interactive surfaces of the sensor chip (not shown) is brought in contact with surfaces (330), (332), (334) and (336). In this manner, the same or different MALDI matrix (or matrices) may be applied to the individual interactive surfaces of the IA sensor chip. *Alternatively, an ink-jet applicator may be employed, wherein the reservoir or "ink" of the applicator is the MALDI matrix. In this manner, the individual interactive layers of an IA sensor may be individually contacted with the MALDI matrix*" (col. 10, lines 5-23). Furthermore, **"samples and reagents are delivered to the chip surface in regulated low volumes by a fully automated delivery flow system"** (col. 8, lines 43-45).

It would have been obvious for anyone of ordinary skill in the art to modify Zhang's method for preparing MALDI-MS matrix by using plurality of vesicles in forms of capillaries, as disclosed by Zhang, or in form of pins (ink-jet applicators), with full automation of the fluid delivery, as disclosed by Nelson, because this is an obvious advantage regarding the speed and efficiency of the method of forming MALDI-MS substrate.

Although Zhang in view of Nelson do not specifically disclose TOF-MS analysis, it would have been obvious for anyone of ordinary skill in the art to use Zhang-Nelson's substrate for TOF-MS analysis, which also comprises desorbing the analyte from the matrix on the substrate.

11. **Claims 5, 45-46, 48-50 and 78** are rejected under 35 U.S.C. 103 (a) as being unpatentable over Zhang in view of Nelson, as applied to claims 11-13, 31-34, 40-43, 47, 51, 54-59, 64-72, 82-85 and 87-94 above, and further in view of Zhang et al. (J. Mass Spectrom.) (Zhang-2).

Zhang in view of Nelson do not specifically disclose preliminary disposition of the matrix material on the substrate with following ejection of the solution of the analyte into the same spots.

Zhang-2 teaches "continuous deposition on a matrix-precoated membrane target" for "capillary electrophoresis combined with MALDI-MS spectrometry".

It would have been obvious for anyone of ordinary skill in the art to slightly modify Zhang-Nelson's method by first placing matrix into the locations of the substrate, i.e. precoating the locations with the matrix the way taught by Zhang-2, and then depositing solution of the analyte into these locations, because Zhang-2 demonstrated the efficiency of such sequence in depositing the material. Although Zhang-2 does not teach the reverse disposition of the material on the substrate because of the specifics of his method, it would have been obvious for anyone of ordinary skill in the art to do so, because the main purpose of depositing a solution of the matrix and a solution of the analyte on the substrate is mixing the matrix and the analyte on the substrate, so the sequence of such deposition does not play much role if the right solvents are chosen by a routine experimentation.

12. **Claims 16-24 and 102-103** are rejected under 35 U.S.C. 103 (a) as being unpatentable over Zhang in view of Hancock et al. (US 5,716,825, IDS).

Zhang does not specifically disclose a material of the substrate or the nature of the wells of the multi-well sample holder.

Hancock discloses an integrated nucleic acid analysis system for MALDI-TOF MS, and describes in particular a thin film sample support, which is a substantially "planar manifold made of a non-conducting material that includes a microchannel and other necessary components of a

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miniturized sample preparation compartment, an interface to non-consumable parts, and an ionization surface for MALDI-TOF MS. Such a miniaturized device may be formed from a variety of materials (e. g., **silicon, glass, low cost polymers**) by techniques that are well known in the art (e.g., micromachining, chemical etching, laser ablation, and the like)" (col. 4,11. 34-44). Hancock further describes a process wherein analyte is embedded in a solid or crystalline "matrix" of light-absorbing molecules (e. g., **nicotinic, sinapinic, or 3-hydroxypicolinic acid**) (col. 6,11. 15-25). Hydrophobic and hydrophilic MALDI ionization surfaces, such as metals (**gold, copper, stainless steel**), glass, silica, nylon and other synthetic polymers, agarose and other carbohydrate polymers, and plastics are disclosed as surfaces for actively capturing analyte (col. 6,11. 38-44). Other capture regions are disclosed, such as **surface of a bead, particle** or planar support treated with a bifunctional cross-linking reagent. "According to the practice of the present invention, a capture region may be formed in any microstructure surface in the sample preparation compartment by linking an analyte binding partner directly to the surface, and on MALDI ionization surfaces integrated with the preparation compartment. Alternatively, a capture region may be formed on the surfaces of beads, which can be chemically attached to the surface of the support, or magnetically attached by using magnetically responsive beads and applying a magnetic field to anchor the beads to the desired region of the support. Magnetically responsive beads and particles are well-known in the art and are commercially available from, for example, Dynal.RTM., Inc. (Lake Success, N.Y.) and Bangs Laboratories, Inc. (Carmel, Ind.)" (col. 7, 11. 30-43).

It would have been obvious at the time the invention was made to a person having ordinary skill in the art to use any of the materials described by Hancock for Zhang's multi-well sample support (substrate), because Hancock gives more detailed description of the materials used for the preparation of samples for MALDI-MS analysis of DNA, including the support itself, while Zhang concentrates on the method of deposition of 5 nl of the material on this support.

12. **Claims 60, 86 and 104-107** are rejected under 35 U.S.C. 103 (a) as being unpatentable over Zhang in view of Nelson, as applied to claims 11-13, 29, 31-34, 40-43, 47, 51, 54-59, 64-72, 82-85 and 87-94 above, and further in view of Hancock.



While Zhang in view of Nelson do not specifically disclose functionalized substrates, Hancock lists a plurality of possible materials for MALDI-MS substrates, including those recited in claim 86. It would have been obvious for anyone of ordinary skill in the art to use materials disclosed by Hancock in Zhang-Nelson's method, because these are convention materials for MALDI-MS substrates.

### *Response to Arguments*

13. Applicant's arguments filed on 04/12/04 have been fully considered but they are not persuasive.

The arguments related to the rejection of claims 43-44 under 35 U.S.C. 112, first paragraph: the parent claim 40 recites forming a MALDI-MS substrate with an array of spots, "wherein mass spectra of the sample material obtained from each spot are reproducible within the array of spots". Claim 40 recites that this material is contained in the fluid dispensed on the substrate. Claims 43 and 44 recite that the fluid comprises only solvent and the matrix material, without mentioning the sample material. Such recitation does not provide enablement for the method recited in the parent claim 40, since if there is no sample material contained in the fluid, the reproducible MS spectra cannot be obtained, since there are no MS spectra. Claims 43 and 44 are not enabled in the form they are written. Further steps of adding analyte material to the spots should be added to the method recited in claims 43 and 44 to make them enabled.

In arguments related to the rejection of claims 1-4, 6, 9-10, 14-15, 25-28 and 30 under 35 U.S.C. 102(b) the Applicant asserts that "Zhang et al. does not describe deposition of defined and controlled volumes nor disclose a method that requires such precision in sample deposition, not in a high throughout analyses requiring reproducibility among mass spectra on an array on single surface". This is in a complete contradiction to Zhang's disclosure, cited twice by the examiner in two Office actions: "into **each** well [which assumes *an array* of wells] was dispensed 20 droplets (~ 5 **nL**) of 3-HPA matrix solution" (page 26, the last paragraph). Citing the examiner's statement again: "Zhang specifically indicates, "it is clear that sample preparation for MALDI analysis is a critical step in achieving high sensitivity and **reproducibility** for biological mixtures" (page 1771, left column). By the preparation of the sample he means

removal of salts for highly salted analytes and *decreasing the volume of the sample*, with ~ 5 nL of the volume confirming high reproducibility of the experimental data, which comprise MALDI-MS spectra parameters”. Zhang is dealing with an array of precisely deposited small volume droplets (~ 5 nL, exactly the same precision of the volume of droplets disclosed in the instant application), indicating reproducibility and high sensitivity of such arrays for MALDI analysis. The examiner does not quite understand, how is it possible to interpret an absolutely clear and unambiguous disclosure of Zhang to conclude that it “is very different from the instant claims”? How does not Zheng describe or address arrays, when the drawing clearly shows these arrays and Zheng is referring to “each well” of the multi-well substrate? The application of arrays for e.g. high-throughput analysis is irrelevant to the subject matter of the instant application, and therefore does not have any patentable weight. The examiner would like to notice, that “elution of material from the column” creates multiple samples. Again, Zhang does indicate that decreasing the volume of the sample, to e.g. ~ 5 nL, is essential for high sensitivity and reproducibility of MALDI analysis of biological mixtures. The volume indicated is exactly of the same accuracy and precision as the one disclosed in the instant specification. While the Applicant highlighted the word *about* 5 nL, the examiner could not find in the specification any referral to an exact volume of e.g. 5.00 nL. The Applicant’s statements regarding Zheng’s disclosure clearly contradict its essence and cannot be considered reliable. Zheng does teach MALDI analysis from each spot, as no other way of performing MALDI analysis from wells has been invented so far.

“Without contacting”. First, it looks like there is confusion in terminology used by the Applicant. In the beginning of the paragraph the Applicant refers to the contact of a vesicle with a substrate; at the end of the paragraph, referring to Zheng, the Applicant recites contacting eluate with a target (substrate). Vesicle and eluate are quite different things. Vesicle is a dispensing device, while eluate is a dispensed liquid. The examiner has a question to the Applicant: how can the fluid be deposited on the target (substrate) without contacting it? As for contacting the vesicle with the substrate: formation of a droplet (disclosed by Zheng) requires non-contacting interaction between the vesicle and the substrate. Moreover, contacting vesicle with the substrate would lead to the vesicle contamination, the fact obvious for anyone of

ordinary skill in the art. Zheng does not teach contacting vesicle with the substrate, because he discloses formation of a droplet. It is clear for any ordinary person.

Zheng discloses highly precise and reproducible arrays of droplets of  $\sim 5$  nL, the volume disclosed in the instant specification. The Applicant failed to show any evidence that this statement is incorrect. It is not clear to the examiner, why the Applicant addresses the issue of controlling the time length of delivery, which is not the subject matter of the claims.

The next Applicant's argument is so blur that the examiner does not quite understand its essence. For example, what is the difference between dispensing a sample with analyte or without analyte regarding the volume of the droplet?

"Accuracy" and "precision". If multiple droplets are disposed with the same accuracy (the same volume), and it is the volume accuracy that provides reproducibility of the results for different spots, according to the Applicant, then why the same accuracy does not provide the same precision? The Applicant did not provide any explanation of what could be considered a "defined and controlled volume" of the analyte, if  $\sim 5$  nL (which is disclosed by the Applicant as a defined and controlled volume) does not correspond this definition.

It is not quite clear for the examiner how the Applicant's general statement, "improvements in MALDI-MS substrate production are neither basic knowledge nor arise simply from common sense, and methods of MALDI-MS substrate production fall outside of the expertise of the PTO to determine in the absence of supporting evidence", should be interpreted by the examiner. Does it mean that any routineer in the art possesses only "basic knowledge" and "common sense"? This is not a correct definition of a person "skilled in the art". It is not quite clear from this statement, what type of expertise is required to understand the improvement of MALDI substrate, when Zheng teaches a crucial role of small volume ( $\sim 5$  nL) droplets deposited on the substrate for high sensitive and reproducible MALDI analysis? What type of technical knowledge is expected from any person skilled in the art to conclude that in order to obtain reproducible results for MALDI-MS experiment, comprising laser desorption of the sample from the MALDI matrix, the same volume (or aliquots) of the sample material should be deposited on the substrate? The main idea of the instant disclosure is that the volumes of the deposited droplets should be in nL range in order to get reproducible results, not that they should be the same; the latter is obvious for any ordinary person, even the one not skilled in the art. It is

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basically having the same concentration of the analyte within all droplets (or spots). If there is the same amount of the analyte in the droplets, but they have different sizes, then the concentration of the analyte is different in each droplet. How can the reproducible results be obtained in this case?

Again, Zheng discloses the MALDI-MS substrate with reproducible analytical spots, formed by deposition of ~5 nL droplets (the accuracy indicated by the Applicants), with these spots placed as an array (which is clear from the Drawing). *Note:* Zheng does not work with a  $\mu$ L volume range, but rather nL volume range, unlike what the Applicant indicates on pages 21 and 22. Moreover, Zheng absolutely unambiguously indicates that the volume of the sample is essential for reproducibility of the results, again in opposition to what the Applicant claims. The Applicant's questioning of the identical size of the wells in a multi-well substrate disclosed by Zheng goes beyond any reasonable arguments. The examiner would like the Applicant to provide any reference disclosing using conventional multi-well substrates with variable sizes of wells without indicating that specifically. That Zheng's disclosure does not indicate that the same volume of ~ 5 nL is deposited in each well, as mentioned by the Applicant, is simply not true. The examiner recited this quote many times: "into each well was dispensed 20 droplets (~ 5 nL) of 3-HPA matrix solution".

The same arguments regarding Zheng's teaching are repeated over and over again, which does not lead to much progress in clearing the essence of the invention and providing evidence for patentability and unexpected results in respect to the prior art.

"Movement of the vesicle".

The only question that the examiner would like to ask the Applicant, is the following: what possible ways of depositing samples into multiple wells on the multi-well substrate could be proposed by the Applicant, if the vesicle is not moving from well to well?

The examiner finds the Applicant's arguments regarding anticipatory rejection of the claims over Zheng non-persuasive and non-convincing. The same is true for the arguments regarding obviousness-type rejections. Moreover, the examiner finds it unnecessary and burdensome for the examiner to read 40-pages remarks filled with recitation of all possible court cases along with the pending claims, which only obscure the essence of the Applicant's arguments.

Zheng does not disclose depositing the spots from multiple vesicles, which is disclosed by Nelson. Nelson teaches a more complex combined method of surface plasmon spectroscopy with MALDI MS comprising formation of MALDI-MS matrix by using ink-jet applicator. Nelson's method is clearly directed toward high-throughput analysis of multiple samples from multiple spots, with MALDI analysis from each spot being a part of more complicated analytical method than just MALDI-MS analysis. Nowhere does Nelson indicate that ink-jet applicator gets in contact with the substrate with an interactive surface layer for depositing MALDI matrix. It is hard to imagine such an embodiment in Nelson's disclosure, which would lead to contamination of the ink-jet applicator. Zheng does not disclose MALDI substrate specifically for high-throughput analysis, which obviously Nelson does, thus curing deficiency of Zheng's disclosure. It is completely unclear, why ink-jet applicator disclosed by Nelson cannot be applied as improvement of Zheng's method by replacing Zheng's capillary with ink-jet applicator, if the presence of salts is not essential for the material under study? Zheng implies capillary for desalting material with high content of salts, which lower the sensitivity of the analysis. If the sensitivity of the analysis is not a question, changing a singular capillary to the ink-jet applicator, which allows dispensing arrays of the spots at once, is a clear advantage, obvious for any routineer in the art. If the Applicant believes the opposite, more evidence of non-obviousness of such improvement is required.

“Automation”

*In re Venner*, 120 USPQ 192 (CCPA 1958): to provide a mechanical or automatic means to replace manual activity which accomplishes the same result is within the skill of a routineer in the art.

Again, Zheng's “elution” is depositing the sample from the singular capillary, while Nelson's deposition of the matrix involves the ink-jet applicator. Nelson specifically indicates, “samples and reagents are delivered to the chip surface in regulated low volumes by a fully automated delivery flow system”, using ink-jet applicator for delivering MALDI matrix. Nelson's method is more sophisticated and complex, than the one disclosed in the instant application; this, however does not make it non-obvious to use the most general part of the method related to delivery samples to the substrate surface using ink-jet technique, in analogous methods.

In the rest of the arguments the Applicant seems to attack each reference individually, which does not comply with the US patent practice: one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding non-obviousness of the results: the examiner would rather expect non-obviousness of the results, if defined and controlled volumes of the sample material of the same content and concentration would not lead to reproducible results, especially taking into account indication of Zheng that small volume of the sample (~ 5 nL) is essential for sensitivity and reproducibility of MALDI MS spectra.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

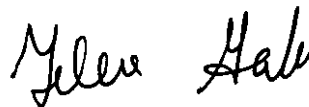
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Yelena G. Gakh  
6/6/04

A handwritten signature in black ink that reads "Yelena Gakh". The signature is written in a cursive, flowing style.